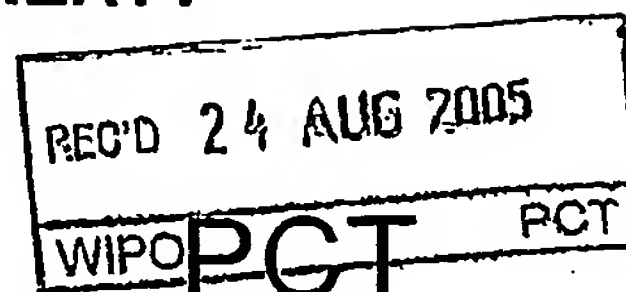


PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2005/001168

International filing date (day/month/year)
04.02.2005

Priority date (day/month/year)
05.02.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/11, C12Q1/68

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Sprinks, M

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001168

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001168

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 11,12,14,15 (partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 11,12,14,15 (partially)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001168

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-18
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-18
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	

2. Citations and explanations

see separate sheet

D1: HACKERMÜLLER J. ET AL.,: "towards a functional classification of ARE protein interactions" GENOME INFORMATICS, vol. 13, 2002, pages 326-327, XP002299091

V) Novelty, inventive step and industrial applicability

Inventive step

- 1) The present application does not satisfy the criterion set forth in **Article 33 (3) PCT** because the subject-matter of **claims 1-18** does not involve an inventive step (**Rule 65.1 and 65.2 PCT**).
- 2) D1 discloses the use of thermodynamic modelling to study the mechanisms of ARE-binding protein interactions. It specifically refers to ELAVL1 (see **claims 2 and 13**), the importance of understanding interference of other AREs with ARE-protein interactions for the selection of drug targets, and ARE binding ELAVL1 analogues.

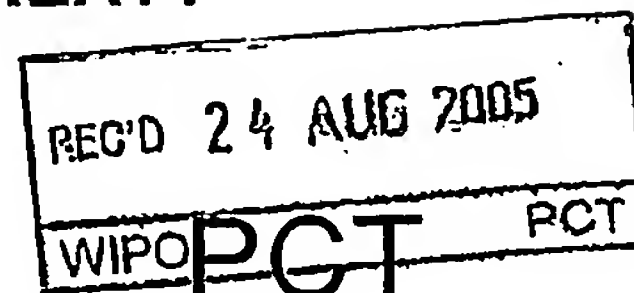
Consequently, the claimed methods and compounds are considered as the straightforward reduction to practice and results of the concepts taught in D1, which result from the combination of the skilled person's desire to modulate any known regulatory ARE-ligand interaction (which may be considered as the technical problem) with the teachings of D1.

- 3) It should be noted that the methods of **claims 5 and 6** do not appear to be restricted to the general concept in **claim 1** of calculating and using thermodynamic probabilities, since the phrase "that changes the thermodynamic probability" appears to refer to an implicit property of an oligonucleotide whose suitability as a modulator would be obvious in any event at the hybridisation step alone.

In such a case, said methods might not be considered novel or even unitary as they could refer to screening assays using known standards (which intrinsically change the thermodynamic probability in any event). However, for the time being, the Applicant is given the benefit of doubt.

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FOR FURTHER ACTION
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International filing date (day/month/year)
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Priority date (day/month/year)
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International Patent Classification (IPC) or both national classification and IPC
C12N15/11, C12Q1/68

Applicant
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3. For further details, see notes to Form PCT/ISA/220.

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Authorized Officer

Sprinks, M

Telephone No. +49 89 2399-7706



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001168

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
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 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
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4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
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3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001168

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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- ☒ claims Nos. 11,12,14,15 (partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
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- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
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 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
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- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001168

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-18
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-18
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	

2. Citations and explanations

see separate sheet

D1: HACKERMÜLLER J. ET AL.,: "towards a functional classification of ARE protein interactions" GENOME INFORMATICS, vol. 13, 2002, pages 326-327, XP002299091

V) Novelty, inventive step and industrial applicability

Inventive step

- 1) The present application does not satisfy the criterion set forth in **Article 33 (3) PCT** because the subject-matter of **claims 1-18** does not involve an inventive step (**Rule 65.1 and 65.2 PCT**).
- 2) D1 discloses the use of thermodynamic modelling to study the mechanisms of ARE-binding protein interactions. It specifically refers to ELAVL1 (see **claims 2 and 13**), the importance of understanding interference of other AREs with ARE-protein interactions for the selection of drug targets, and ARE binding ELAVL1 analogues.

Consequently, the claimed methods and compounds are considered as the straightforward reduction to practice and results of the concepts taught in D1, which result from the combination of the skilled person's desire to modulate any known regulatory ARE-ligand interaction (which may be considered as the technical problem) with the teachings of D1.

- 3) It should be noted that the methods of **claims 5 and 6** do not appear to be restricted to the general concept in **claim 1** of calculating and using thermodynamic probabilities, since the phrase "that changes the thermodynamic probability" appears to refer to an implicit property of an oligonucleotide whose suitability as a modulator would be obvious in any event at the hybridisation step alone.

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